Claims 1-16 and 20-22 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard for Written Description

The first paragraph of 35 U.S.C. § 112 sets forth the written description requirement for patents as follows:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The standard regarding what is or is not supported by the specification has been clearly articulated as "requiring the specification to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventor was in possession of the invention", i.e., whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111, 1117 (Fed . Cir. 1991). Compliance with the written description requirement is essentially a fact-based inquiry that will "necessarily vary depending on the nature of the invention claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (citing *In re DiLeone*, 436 F.2d

1404, 1405 (CCPA 1971)). Satisfaction of the written description requirement is determined on a case-by-case basis.

The inquiry into whether or not there is an adequate written description is not performed in a vacuum. "Knowledge of one skilled in the art is relevant to meeting [the written description] requirement." *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. Apr. 2, 2002) (slip op.). This fact has implications not only for validity challenges, but also for patent prosecution. *See In re Alton*, 76 F.3d 1168, 1174-75 (Fed. Cir. 1996).

In the most recent CAFC decision, *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. July 15, 2002), the Federal Circuit vacated a prior decision, *Enzo Biochem, Inc. v. Gen-Probe*, 285 F.3d 1013, 62 USPQ 2d 1289 (Fed. Cir. April 2, 2002), and reversed the district court's grant of summary judgment that Enzo's claims are invalid for failure to meet the written description requirement, stating in relevant part:

"It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement. The PTO has issued Guidelines governing its internal practice for addressing that issue. The Guidelines, like the Manual of Patent Examining Procedure ("MPEP"), are not binding on this court, but may be given judicial notice to the extent they do not conflict with the statute. See Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180 n.10, 33 USPQ2d 1823, 1828 n.10 (Fed. Cir. 1995). In its Guidelines, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, ***other physical and/or chemical properties, functional characteristics when coupled***

with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added). For example, the PTO would find compliance with § 112, ¶ 1, for a claim to an "isolated antibody capable of binding to antigen X," notwithstanding the functional definition of the antibody, in light of "the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/patents/guides.htm ("Application of Guidelines").

The general principle of the written description requirement for a claimed genus may be satisfied through (1) sufficient description of ***a representative number of species*** by actual reduction to practice, (2) reduction to drawings of a general structure, or (3) disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, (4) describing functional characteristics coupled with a known or disclosed correlation between function and structure, or (5) a combination of such identifying characteristics, sufficient to show the appellant was in possession of the claimed genus. Reagents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

There is no legal requirement that an inventor have actually reduced the invention to practice prior to filing. MPEP at § 2164.02, *citing* Gould v. Quigg, 822 F.2d 1074 (Fed. Cir. 1987). "The specification need not contain an example if the invention is otherwise disclosed in

such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *Id.*

With regard to post-filing art, the CAFC stated in In re Brana, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995), that a post-filing date declaration setting forth test results substantiating utility "pertains to the accuracy of a statement already in the specification. . . . It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed." An important distinction has been made by the Courts between evidence of the knowledge and ability of those of skill in the art at the time of filing and evidence to prove that statements made in the application are correct. In the former case, of course, only evidence which existed prior to the filing of the application, or evidence that certain knowledge existed at the time of filing, is admissible (In re Hogan, 194 USPQ 527 (CCPA 1977)). In the latter case, as in this case, any evidence, developed at any time, may be submitted for consideration.

The clearest affirmation of the seasonability of factual evidence developed after the filing date of an application is provided by the Court in In re Marzocchi (169 USPQ 367, 370 (CCPA 1971)). In discussing rejections under 35 USC 112 where an examiner asserts that the unpredictability of the art creates a reasonable doubt as to the accuracy of a particular broad statement (in the application) supporting enablement, the Court states:

> Most often, additional factors, such as the teachings of pertinent references[*], will be available to substantiate any doubts that the asserted scope of enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof.

***

Not necessarily *prior* art references, it should be noted, since the question would be regarding the *accuracy* of a statement in the specification, not whether that statement had been made before. [emphasis in the original]

Id. at 367

In *In re Wilson* (135 USPQ 442, 444 (CCPA 1962)), the Court agreed that a reference, published after the filing date of the application, was properly cited to show a state of fact. In *In re Langer* (183 USPQ 288, 297 (CCPA 1974)), the Court again noted that later published references "are properly cited for the purpose of showing a fact." In *In re Rainer* (134 USPQ 343, 345 (CCPA 1962)) the Court found no error in the limited use made of a reference published after Applicant's filing date to show a fact. While all of these cases involved publications cited by the Patent Office in support of rejections, the same standard applies to evidence cited by Applicants. See In re Hogan.

It is not necessary, nor is it required, that each element of the claimed invention be within a single post filing art reference. It is the evidence as a whole that must be considered. Elements of the claimed invention *independently* described in the post filing art, can cumulatively demonstrate the feasibility of reducing the invention to practice using materials and methods described in the specification and/or known by a skilled artisan as of the time of filing.

The Specification Complies with the Written Description Requirement

The first basis for the rejection is the allegation that the specification only describes a small number of specific compounds which act via SR-BI including estrogen, see example 3; adenoviral vector encoding SR-BI, see example 5; and anti-SR-BI antibody, see example 8.

This in itself seems to provide broad support for a genus claim, since it shows actual reduction to practice with three widely disparate types of compounds: a small inorganic molecule, a nucleotide molecule in a vector, and an antibody. Moreover, all of these compounds alter fertility by altering lipoprotein, LDL, HDL or cholesterol levels.

However, the requirement for a written description is **not** a requirement that applicants reduce to practice **all** of the species that may fall within the claimed genus. In this regard, in addition to the three examples showing actual reduction to practice, the examiner's attention is drawn to the extensive list of molecules beginning at page 11, under the section entitled "I. Inhibitors of SR-BI transport of cholesterol." and page 12, under the section entitled "II. Methods of Regulation of SR-BI cholesterol transport to alter steroidogenesis", with sub-sections for nucleotide molecules, and other molecules which alter SR-BI binding or expression (page 14) as well as the actual assays for modified LDL uptake, binding and degradation (page 15), Northern blot for expression in tissues (page 16 and pages 17-18), HDL binding (pages 16-17), methods for screening of libraries for small organic molecules (pages 18-19), methods for designing drugs (pages 19-20), methods for obtaining nucleic acid regulators (pages 20-23), SR-BI receptor fragments (pages 24-25). Together, this description clearly conveys to those skilled in the art that, in addition to the classes of compounds actually used to show reduction to

practice, a number of other molecules were known and could be screened for utility in the claimed method.

In contrast to the examiner's assertion that there is no mention in the specification of fertility treatment by altering levels of serum cholesterol, example 6, page 45-54 of the specification, using the SR-BI knockout mouse, demonstrates that manipulation of the serum cholesterol in fact alters the fertility of the mouse. Further evidence was provided with the previously submitted response. See Miettinen, et al. J. Clinic. Invest. 108:1717-1722 (2001).

The applicants demonstrate in Miettinen that the mice are infertile because they have altered levels of lipoproteins and that fertility can be restored by further altering these lipoprotein levels. In the SR-BI knockout, the serum cholesterol levels increase two fold and the HDL particles become abnormally large. By changing the conformation of the lipoprotein using probucol, fertility was restored. The loss of ApoA1 plays a role in lowering HDL cholesterol but is not essential for fertility. Clearance of serum cholesterol still occurs and can be increased by overexpression of SR-BI via viral vector. In the ApoA1 knockout, ApoE becomes the major apolipoprotein component of HDL and increases in expression. ApoE has recently been shown to be a ligand for SR-BI and that SR-BI functions directly in clearing cholesterol from HDL. Miettinen also teach that SR-BI is not required for fertility in the absence of ApoA1 during embryonic development, adult maturation or ovarian function. In the combined knockout, cholesterol levels are such that functional oocytes can develop in the altered extraovarian environment wherein the proper window of serum cholesterol and lipoprotein complement exists for conception and implantation.

The mechanism has been described as the ovum viability and success of implantation is dependent on state of HDL and by altering this factor pharmacologically, fertility can be restored. The infertility seen in SR-BI mice is not due to malformation of the reproductive organs but an inability to produce functional oocytes in what can be considered a growth restricted, hostile environment. This was evidenced by the successful conception after transplantation of SR-BI -/-ovaries into wild-type mice almost immediately. Fertility was restored by treating pharmacologically with probucol or genetically by ablating ApoA-1 expression.

With respect to the statement that applicants have not provided adequate written description that modulation of SR-BI would be required to treat "any and all" reproductive disorders, applicants have not claimed treating "all" reproductive disorders, but " A method for altering fertility or treating a reproductive disorder in a mammal comprising administering a compound altering lipoprotein, LDL, HDL or cholesterol levels in the mammal". Note that while the claims encompass humans, there is no requirement that the claim be specific to the treatment of humans, and mice are considered appropriate animal models of human fertility (or at least most of the drugs used for contraception were tested initially in mice). As to issue of tissue distribution, the examiner's attention is drawn to page 10, for example, and the figures, which demonstrate that it is the levels in the steroidogenic tissues that is most important, but that levels may also be altered in other tissues.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-16 and 20-22 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claims 1-16 and 20-22 are not incomplete. The only step that is required for treatment is defined by the claims: a compound altering altering lipoprotein, LDL, HDL or cholesterol levels in the mammal is administered to the animal. The claims have been amended to recite that the compound must be administered in an effective dosage, and that the mammal must be in need of treatment thereof.

Claim 1 has also been amended to recite that the animal is female.

Claims 2 and 4-7 have been amended to provide antecedent basis.

Double Patenting

The claims have been rejected under the doctrine of obviousness-type double patenting over claims 1-10 of U.S. Patent No. 5,962,322. This rejection is respectfully traversed.

The claims of this application require treatment of a mammal for a reproductive disorder or to alter fertility; there is no mention of such a condition in the claims of the '322 patent. There is no expectation that the method of the '322 patent would be of any use in treating such conditions, much less to select only female patients for such treatment. Accordingly, the claims in the '322 patent do not make obvious the claims now pending in this application.

Rejection Under 35 U.S.C. § 102

Claims 1-7, 15 and 16 were rejected under 35 U.S.C. § 102(a) as disclosed by Rigotti, et al., Cur. Opin. Lipid. 8:181-188 (1997); Rigotti, et al. J. Biol. Chem. 271:33545-33549. Claims 1, 2, 4, 5, 8, 15 and 16 were rejected under 35 U.S.C. 102(a) as disclosed by Spona, et al., Contraception 54:299-304 (1996). Claims 1, 2, 4, 5, 9, 12, 13, and 15 were rejected under 35 U.S.C. 102(b) as disclosed by Bajetta, et al., Br. J. Cancer 70, 145-150 (1994). Claims 1, 2, 4, 5, 9, 12, 14, and 15 were rejected under 35 U.S.C. 102(b) as disclosed by Cirkel, Medical Treatment of symptomatic endometriosis, Human Reproduction 11, 89-101 (1996). Claims 1, 2, 4, 5, 10, 11, 15 and 16 were rejected under 35 U.S.C. 102(b) as disclosed by Whitcroft, et al. Clin. Endocrinol. 36, 15-20 (1992). Claim 1 has been rejected under 35 U.S.C. 102(e) over U.S. patent No. 5,674,488 to Reich. Applicants respectfully traverse these rejections to the extent that they are applied to the claims as amended. Claims 11, 13 and 14 have been cancelled.

Rigotti, et al. Papers

Neither Rigotti, et al. paper discloses administration of a compound altering LDL, HDL or cholesterol to a female mammal in need of treatment for a reproductive disorder or to alter fertility. Rigotti, et al., discloses transient overexpression of SR-BI in normal mice (page 185, col. 1). Rigotti, et al. reports that administration of estrogen to normal rats increases SR-BI protein expression in the steroidogenic cells (page 183, col. 2; J. Biol. Chem.). Rigotti, et al., also reports that there are higher levels of naturally occurring, unstimulated SR-BI in the liver, the adrenal gland and the ovary, and the mammary glands of pregnant rats (page 183, col. 1). However, since neither Rigotti, et al. discloses administration of compounds to animals in need

of treatment for reproductive disorders or to alter fertility, neither Rigotti, et al. discloses the claimed subject matter.

Spona

Spona does not disclose administering an effective amount of a compound which alters LDL, HDL or cholesterol to a mammal in need of treatment of a reproductive disorder or to alter fertility. Spona discloses administering an oral contraceptive to normal human females. There is no measurement of any lipid values and the examiner has produced no evidence that an oral contraceptive in the dosage used by Spona would alter LDL, HDL or cholesterol levels. It is well known there are many mechanisms by which fertility can be affected, and one cannot assume that a contraceptive would inherently alter LDL, HDL or cholesterol levels - indeed, such information would need to be made available on a package insert since this is a prescription product, and no such information is present, as shown by the accompanying package insert. See also the paper a page 299, bottom of col 2, which states that "The monophasic preparation...has been observed in a number of studies to be metabolically balanced in terms of lipid and carbohydrate metabolism...".

Bajetta, et al.

Bajetta et al. describes administration of formestane to breast cancer patients. The claims which read on cancer have been cancelled, since cancer is not normally considered a reproductive disorder. On this basis alone, Bajetta does not anticipate the amended claims. However, there is also no evidence that Bajetta alters LDL, HDL or cholesterol levels. A search

of both Medline and the NIH website failed to find any article or reference to alteration of lipid by formestane.

Cirkel

Cirkel describes various treatments for endometriosis, which is an overgrowth of endometrial tissues, which according to Cirkel, may not even be a disease. The dependent claim to endometriosis has been cancelled, again on the basis that it is a disease more like a cancer than a reproductive disorder. The treatments include various hormones, including progestogens, danazol and LHRH agonists. There is no disclosure of administering an amount which is effective to alter LDL, HDL or cholesterol levels. Not surprisingly, the entire article focuses on objective relief from symptoms, including pain and various accompanying hormonal changes.

There is no basis for asserting that merely administering a compound such as estrogen will achieve the intended effect: the dosage must be correct, as well as the selection of drug, to meet the claimed limitations. Absent some disclosure as to the need to look to lipid levels, one would not inherently achieve the desired result. Moreover, a review of the literature does not find any association with the pharmaceutically acceptable levels of these compounds in the treatment of endometriosis with changes in lipid level - i.e., these compounds are not effective due to alterations in LDL, HDL or cholesterol levels.

Whitcroft and Stevenson

Whitcroft and Stevenson is much like Cirkel - it discloses the use of hormone replacement therapy (although as the recent studies have demonstrated, the risks are now thought to outweigh the benefits for women with intact uteruses). The HRT they use is designed to

maintain bone mass; not to treat reproductive disorders or alter fertility. The dependent claim to treatment of menopause has been cancelled. Moreover, as noted at the bottom of page 16, since HRT is a combination of estrogen and progesterone, any alteration in lipid profile by the estrogen is neutralized by the progesterone. Accordingly, Whitcroft and Stevenson are administering drug (combination of estrogen with progesterone) that does not alter lipid profile and which is administered to individuals who are not within the claimed class, so Whitcroft and Stevenson does not anticipate the claims.

Reich

As the examiner has noted, Reich does not disclose the treatment of women in need of treatment of a reproductive disorder or alteration in fertility. Since the claims require treatment of this population, Reich cannot disclose the claimed method.

Allowance of claims 1-10, 12, 15, 16, and 19-22, as amended, is respectfully solicited.

Respectfully submitted,

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Certificate of Facsimile Transmission

I hereby certify that this Amendment and any documents referred to therein as attached, are being filed with the Assistant Commissioner of Patents by facsimile transmission on August 13, 2002.

Patrea Pabst

U.S.S.N. 09/148,012
Filed: September 4, 1998
MARKED UP VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

Marked Up Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Five times amended) A method for altering fertility or treating a reproductive disorder in a female mammal in need of treatment thereof comprising

administering a compound altering lipoprotein, LDL, HDL or cholesterol levels in the mammal in an amount effective to alter fertility or treat a reproductive disorder in the mammal.

2. The method of claim 1 wherein the compound alters SR-BI expression in the tissue.

3. The method of claim 1 wherein the compound alters binding of SR-BI to high density lipoprotein including cholesteryl ester or other lipoproteins.

4. (amended) The method of claim 2 wherein the compound decreases SR-BI expression in [the] a tissue of the mammal.

5. (amended) The method of claim 2 wherein the compound increases SR-BI expression in [the] a tissue of the mammal.

6. (amended) The method of claim 3 wherein the compound decreases SR-BI binding to lipoprotein or transfer of cholesteryl ester in [the] a tissue of the mammal.

7. (amended) The method of claim 3 wherein the compound increases SR-BI binding to lipoprotein or transfer of cholesteryl ester in [the] a tissue of the mammal.

8. The method of claim 1 wherein the mammal is a female and the compound is administered in an amount effective to prevent normal reproductive function.

9. (amended) The method of claim 1 wherein the mammal has a disorder characterized by an overproduction of steroids.

U.S.S.N. 09/148,012
Filed: September 4, 1998
CLEAN VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

Sub F1

10. (amended) The method of claim 1 wherein the mammal has a disorder characterized by an underproduction of steroids.

Please cancel claim 11.

12. The method of claim 1 wherein the mammal has a disorder which can be treated by decreasing production of steroids.

Please cancel claims 13 and 14.

15. The method of claim 1 wherein the compound differentially alters the activity of, or expression of, SR-BI in different tissues.

16. The method of claim 11 wherein the compound increases SR-BI expression in reproductive tissues and decreases or does not increase SR-BI expression in liver.

19. The method of claim 1 wherein the compound is an antibody to SR-BI.

20. The method of claim 1 wherein the compound is a drug that decreases production of steroids via selective binding to SR-BI.

21. The method of claim 20 wherein the compound decreases cholesterol levels to decrease steroid levels.

22. The method of claim 21 wherein the compound inhibits cholesterol transport.

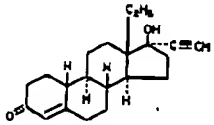
ALESSE® 28 TABLETS
(levonorgestrel and ethinyl estradiol tablets)

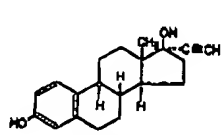
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Description

21 pink active tablets each containing 0.10 mg of levonorgestrel, d(-)-13β-ethyl-17α-ethinyl-17β-hydroxygon-4-en-3-one, a totally synthetic progestogen, and 0.02 mg of ethinyl estradiol, 17α-ethinyl-1,3,5(10)-estratriene-3, 17β-diol. The inactive ingredients present are cellulose, hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, polacrilin potassium, polyethylene glycol, titanium dioxide, and wax E.

7 light-green inert tablets, each containing cellulose, FD&C blue no. 1, hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, polacrilin potassium, polyethylene glycol, titanium dioxide, and wax E.


Levonorgestrel


Ethinyl Estradiol

Clinical Pharmacology

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

PHARMACOKINETICS

Absorption

No specific investigation of the absolute bioavailability of Alesse in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is between 38% and 48%.

After a single dose of Alesse to 22 women under fasting conditions, maximum serum concentrations of levonorgestrel are 2.8 ± 0.9 ng/mL (mean ± SD) at 1.6 ± 0.9 hours. At steady state, attained from day 19 onwards, maximum levonorgestrel concentrations of 6.0 ± 2.7 ng/mL are reached at 1.5 ± 0.5 hours after the daily dose. The minimum serum levels of levonorgestrel at steady state are 1.9 ± 1.0 ng/mL. Observed levonorgestrel concentrations increased from day 1 (single dose) to days 6 and 21 (multiple doses) by 34% and 96%, respectively (Figure 1). Unbound levonorgestrel concentrations increased from day 1 to days 6 and 21 by 25% and 83%, respectively. The kinetics of total levonorgestrel are non-linear due to an increase in binding of levonorgestrel to sex hormone binding globulin (SHBG), which is attributed to increased SHBG levels that are induced by the daily administration of ethinyl estradiol.

Following a single dose, maximum serum concentrations of ethinyl estradiol of 62 ± 21 pg/mL are reached at 1.5 ± 0.5 hours. At steady state, attained from at least day 6 onwards, maximum concentrations of ethinyl estradiol were 77 ± 30 pg/mL and were reached at 1.3 ± 0.7 hours after the daily dose. The minimum serum levels of ethinyl estradiol at steady state are 10.5 ± 5.1 pg/mL. Ethinyl estradiol concentrations did not increase from days 1 to 6, but did increase by 19% from days 1 to 21 (Figure 1).

FIGURE 1
Mean (SE) levonorgestrel and ethinyl estradiol serum concentrations in 22 subjects receiving Alesse (100 µg levonorgestrel and 20 µg ethinyl estradiol)

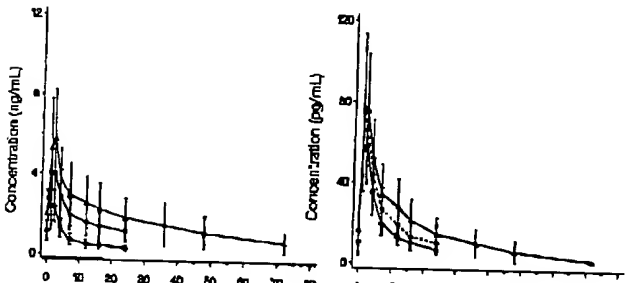


Table I provides a summary of levonorgestrel and ethinyl estradiol pharmacokinetic parameters.

TABLE I: MEAN (SD) PHARMACOKINETIC PARAMETERS OF ALESSE OVER A 21-DAY DOSING PERIOD

Day	C_{max} ng/mL	T_{max} h	AUC ng•h/mL	CL/F mL/h/kg	Vλz/F L/kg	SHBG nmol/L
Levonorgestrel						
1	2.75 (0.88)	1.6 (0.9)	35.2 (12.8)	53.7 (20.8)	2.68 (1.09)	57 (18)
6	4.52 (1.79)	1.5 (0.7)	46.0 (18.8)	40.8 (14.5)	2.05 (0.86)	81 (25)
21	6.00 (2.65)	1.5 (0.5)	69.3 (32.5)	28.4 (10.3)	1.43 (0.62)	93 (40)
	pg/mL	h	pg•h/mL	L/h/kg	L/kg	fu %
Unbound Levonorgestrel						
1	51.2 (12.9)	1.6 (0.9)	654 (201)	2.79 (0.97)	135.9 (41.8)	1.92 (0.30)
6	77.9 (22.0)	1.5 (0.7)	794 (240)	2.24 (0.59)	112.4 (40.5)	1.80 (0.24)
21	103.6 (36.9)	1.5 (0.5)	1177 (452)	1.57 (0.49)	78.6 (29.7)	1.78 (0.19)
	pg/mL	h	pg•h/mL	mL/h/kg	L/kg	
Ethinyl Estradiol						

TABLE II: PERCENTAGE OF W[illegible] EXPERIE[illegible] AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF USE OF A CONTRA[illegible] METHO[illegible]

Method	Perfect Use	Typical Use
Levonorgestrel implants	0.05	0.05
Male sterilization	0.1	0.15
Female sterilization	0.5	0.5
Depo-Provera® (injectable progestogen)	0.3	0.3
Oral contraceptives		5
Combined	0.1	NA
Progestin only	0.5	NA
IUD		
Progesterone	1.5	2.0
Copper T 380A	0.6	0.8
Condom (male) without spermicide	3	14
(female) without spermicide	5	21
Cervical cap		
Nulliparous women	9	20
Parous women	26	40
Vaginal Sponge		
Nulliparous women	9	20
Parous women	20	40
Diaphragm with spermicidal cream or jelly	6	20
Spermicides alone (foam, creams, jellies, and vaginal suppositories)	6	26
Periodic abstinence (all methods)	1-9*	25
Withdrawal	4	19
No contraception (planned pregnancy)	85	85

NA - not available

*Depending on method (calendar, ovulation, symptothermal, post-ovulation)

Adapted from Hatcher RA et al., *Contraceptive Technology, 17th Revised Edition*. New York, NY: Ardent Media, Inc., 1998.

In a clinical trial with Alesse (levonorgestrel and ethinyl estradiol tablets), 1,477 subjects had 7,720 cycles of use and a total of 5 pregnancies were reported. This represents an overall pregnancy rate of 0.84 per 100 woman-years. This rate includes patients who did not take the drug correctly. One or more pills were missed during 1,479 (18.8%) of the 7,870 cycles; thus all tablets were taken during 6,391 (81.2%) of the 7,870 cycles. Of the total 7,870 cycles, a total of 150 cycles were excluded from the calculation of the Pearl Index due to the use of backup contraception and/or missing 3 or more consecutive pills.

Contraindications

Combination oral contraceptives should not be used in women with any of the following conditions:
Thrombophlebitis or thromboembolic disorders
A past history of deep-vein thrombophlebitis or thromboembolic disorders
Cerebrovascular or coronary artery disease
Thrombogenic valvulopathies
Thrombogenic rhythm disorders
Diabetes with vascular involvement
Uncontrolled hypertension
Known or suspected carcinoma of the breast
Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
Undiagnosed abnormal genital bleeding
Cholestatic jaundice of pregnancy or jaundice with prior pill use
Hepatic adenomas or carcinomas, or active liver disease, as long as liver function has not returned to normal
Known or suspected pregnancy
Hypersensitivity to any of the components of Alesse.

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral-contraceptive use. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, and stroke), hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as certain inherited or acquired thrombophilias, hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower doses of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of disease, namely, a ratio of the incidence of a disease among oral-contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral-contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiological methods.

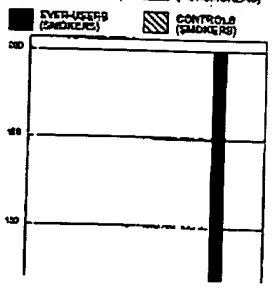
1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. *Myocardial Infarction*

An increased risk of myocardial infarction has been attributed to oral-contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary-artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral-contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

Smoking in combination with oral-contraceptive use has been shown to contribute substantially to the incidence of myocardial infarction in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 (Table III) among women who use oral contraceptives.

CIRCULATORY DISEASE MORTALITY RATES PER 100,000 WOMAN YEARS BY AGE, SMOKING STATUS AND ORAL-CONTRACEPTIVE USE



Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see section 9 in "Warnings"). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. *Thromboembolism*

An increased risk of venous thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep-vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thrombo[illegible]

- INFORMATION FOR THE PATIENT
See Patient Labeling Printed Below.

Adverse Reactions

An increased risk of the following serious adverse reactions (see "Warnings" section for additional information) has been associated with the use of oral contraceptives:

Thromboembolic disorders and other vascular problems (including thrombophlebitis, arterial thromboembolism, pulmonary embolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis), carcinoma of the reproductive organs, hepatic neoplasia (including hepatic adenomas or benign liver tumors), ocular lesions (including retinal vascular thrombosis), gallbladder disease, carbohydrate and lipid effects, elevated blood pressure, and headache.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related:

Nausea
Vomiting
Gastrointestinal symptoms (such as abdominal pain, cramps and bloating)
Breakthrough bleeding
Spotting
Change in menstrual flow
Amenorrhea
Temporary infertility after discontinuation of treatment
Edema/fluid retention
Melasma/chloasma which may persist
Breast changes: tenderness, pain, enlargement, secretion
Change in weight or appetite (increase or decrease)
Change in cervical erosion and secretion
Diminution in lactation when given immediately postpartum
Cholestatic jaundice
Rash (allergic)
Mood changes, including depression
Vaginitis, including candidiasis
Change in corneal curvature (steepening)
Intolerance to contact lenses
Mesenteric thrombosis
Decrease in serum folate levels
Exacerbation of systemic lupus erythematosus
Exacerbation of porphyria
Exacerbation of chorea
Aggravation of varicose veins
Anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:

Premenstrual syndrome
Cataracts
Optic neuritis, which may lead to partial or complete loss of vision
Cystitis-like syndrome
Nervousness
Dizziness
Hirsutism
Loss of scalp hair
Erythema multiforme
Erythema nodosum
Hemorrhagic eruption
Impaired renal function
Hemolytic uremic syndrome
Budd-Chiari syndrome
Acne
Changes in libido
Colitis
Pancreatitis
Dysmenorrhea

Overdosage

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

Noncontraceptive Health Benefits

The following noncontraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral-contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.

Effects on menses:
Increased menstrual cycle regularity
Decreased blood loss and decreased incidence of iron-deficiency anemia
Decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation:
Decreased incidence of functional ovarian cysts
Decreased incidence of ectopic pregnancies

Effects from long-term use:
Decreased incidence of fibroadenomas and fibrocystic disease of the breast
Decreased incidence of acute pelvic inflammatory disease
Decreased incidence of endometrial cancer
Decreased incidence of ovarian cancer

Dosage and Administration

To achieve maximum contraceptive effectiveness, Alesse® (levonorgestrel and ethinyl estradiol tablets) must be taken exactly as directed and at intervals not exceeding 24 hours. The dispenser should be kept in the wallet supplied to avoid possible fading of the pills. If the pills fade, patients should continue to take them as directed.

The dosage of Alesse-28 is one pink tablet daily for 21 consecutive days, followed by one light-green inert tablet daily for 7 consecutive days, according to the prescribed schedule.

It is recommended that Alesse-28 tablets be taken at the same time each day.

Sunday start:

During the first cycle of medication, the patient is instructed to begin taking Alesse-28 on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first tablet (pink) is taken that day. One pink tablet should be taken daily for 21 consecutive days, followed by one light-green inert tablet daily for seven consecutive days. Withdrawal bleeding should usually occur within three days following discontinuation of pink tablets and may not have finished before the next pack is started. During the first cycle, contraceptive reliance should not be placed on Alesse-28 until a pink tablet has been taken daily for 7 consecutive days and a nonhormonal back-up method of birth control should be used during these 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient begins her next and all subsequent 28-day courses of tablets on the same day of the week (Sunday) on which she began her first course, following the same schedule: 21 days on pink tablets — 7 days on light-green inert tablets. If in any cycle the patient starts tablets later than the proper day, she should protect herself against pregnancy by using another method of birth control until she has taken a pink tablet daily for 7 consecutive days.

Day 1 start:

During the first cycle of medication, the patient is instructed to begin taking Alesse-28 during the first 24 hours of her period (day one of her menstrual cycle). One pink tablet should be taken daily for 21 consecutive days, followed by one light-green inert tablet daily for seven consecutive days. Withdrawal bleeding should usually occur within three days following discontinuation of pink tablets and may not have finished before the next pack is started. If medication is begun on day one of the menstrual cycle, no back-up contraception is necessary. If Alesse-28 tablets are started later than day one of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on Alesse-28 tablets until after the first 7 consecutive days of administration and a nonhormonal back-up method of birth control should be used during those 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

When the patient is switching from a 21-day regimen of tablets, she should wait 7 days after her last tablet before she starts Alesse. She will probably experience withdrawal bleeding during that week. She should be sure that no more than 7 days pass after her previous 21-day regimen. When the patient is switching from a 28-day regimen of tablets, she should start her first pack of Alesse on the day after her last tablet. She should not wait any days between packs. The patient may switch any day from a progestin-only pill and should begin Alesse the next day. If switching from an implant or injection, the patient should start Alesse on the day of implant removal or, if using an injection, the day the next injection would be due. In switching from a progestin-only pill, injection or implant, the patient should be advised to use a nonhormonal back-up method of birth control for the first 7 days of tablet-taking.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting, may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and do not smoke. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences. Women with migraine also may be at increased risk of stroke.

2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or health-care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics, and possibly St. John's wort, may decrease oral-contraceptive effectiveness.

Breast cancer has been diagnosed slightly more often in women who use the pill than in women of the same age who do not use the pill. This very small increase in the number of breast cancer diagnoses gradually disappears during the 10 years after stopping use of the pill. It is not known whether the difference is caused by the pill. It may be that women taking the pill were examined more often, so that breast cancer was more likely to be detected.

Some studies have found an increase in the incidence of cancer or precancerous lesions of the cervix in women who use the pill. However, this finding may be related to factors other than the use of the pill.

Taking the pill provides some important noncontraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your health-care provider. Your health-care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health-care provider believes that it is appropriate to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information leaflet gives you further information which you should read and discuss with your health-care provider.

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DETAILED PATIENT LABELING

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

INTRODUCTION

Any woman who considers using oral contraceptives (the birth-control pill or the pill) should understand the benefits and risks of using this form of birth control. This leaflet will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this leaflet is not a replacement for a careful discussion between you and your health-care provider. You should discuss the information provided in this leaflet with him or her, both when you first start taking the pill and during your revisits. You should also follow your health-care provider's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than other nonsurgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1.0% per year when used perfectly, without missing any pills. Average failure rates are 5% per year. The chance of becoming pregnant increases with each missed pill during the menstrual cycle. In comparison, average failure rates for other methods of birth control during the first year of use are as follows:

TABLE: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF USE OF A CONTRACEPTIVE METHOD

Method	Perfect Use	Average Use
Levonorgestrel implants	0.05	0.05
Male sterilization	0.1	0.15
Female sterilization	0.5	0.5
Depo-Provera® (injectable progestogen)	0.3	0.3
Oral contraceptives		5
Combined	0.1	NA
Progestin only	0.5	NA
IUD		
Progesterone	1.5	2.0
Copper T 380A	0.6	0.8
Condom (male) without spermicide	3	14
(female) without spermicide	5	21
Cervical cap		
Never given birth	9	20
Given birth	26	40
Vaginal Sponge		
Never given birth	9	20
Given birth	20	40
Diaphragm with spermicidal cream or jelly	6	20
Spermicides alone (foam, creams, jellies, and vaginal suppositories)	6	26
Periodic abstinence (all methods)	1-9*	25
Withdrawal	4	19
No contraception (planned pregnancy)	85	85

NA - not available

*Depending on method (calendar, ovulation, symptothermal, post-ovulation)

Adapted from Hatcher RA et al., *Contraceptive Technology, 17th Revised Edition*. New York, NY: Ardent

U.S.S.N. *
Filed: *
MARKED UP VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

Clean Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Five times amended) A method for altering fertility or treating a reproductive disorder in a female mammal in need of treatment thereof comprising

E1

administering a compound altering lipoprotein, LDL, HDL or cholesterol levels in the mammal in an amount effective to alter fertility or treat a reproductive disorder in the mammal.

2. The method of claim 1 wherein the compound alters SR-BI expression in the tissue.

3. The method of claim 1 wherein the compound alters binding of SR-BI to high density lipoprotein including cholesteryl ester or other lipoproteins.

4. (amended) The method of claim 2 wherein the compound decreases SR-BI expression in a tissue of the mammal.

5. (amended) The method of claim 2 wherein the compound increases SR-BI expression in a tissue of the mammal.

E2

6. (amended) The method of claim 3 wherein the compound decreases SR-BI binding to lipoprotein or transfer of cholesteryl ester in a tissue of the mammal.

7. (amended) The method of claim 3 wherein the compound increases SR-BI binding to lipoprotein or transfer of cholesteryl ester in a tissue of the mammal.

8. The method of claim 1 wherein the mammal is a female and the compound is administered in an amount effective to prevent normal reproductive function.

9. (amended) The method of claim 1 wherein the mammal has a disorder characterized by an overproduction of steroids.

E3

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E3

10. (amended) The method of claim 1 wherein the mammal has a disorder characterized by an underproduction of steroids.

12. The method of claim 1 wherein the mammal has a disorder which can be treated by decreasing production of steroids.

15. The method of claim 1 wherein the compound differentially alters the activity of, or expression of, SR-BI in different tissues.

16. The method of claim 11 wherein the compound increases SR-BI expression in reproductive tissues and decreases or does not increase SR-BI expression in liver.

19. The method of claim 1 wherein the compound is an antibody to SR-BI.

20. The method of claim 1 wherein the compound is a drug that decreases production of steroids via selective binding to SR-BI.

21. The method of claim 20 wherein the compound decreases cholesterol levels to decrease steroid levels.

22. The method of claim 21 wherein the compound inhibits cholesterol transport.

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